

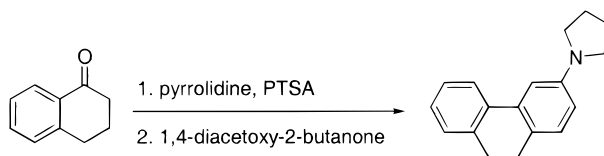
Formation of Aromatic Rings through
Enamine AnnulationChen Wang and Harold Kohn^{*,†}

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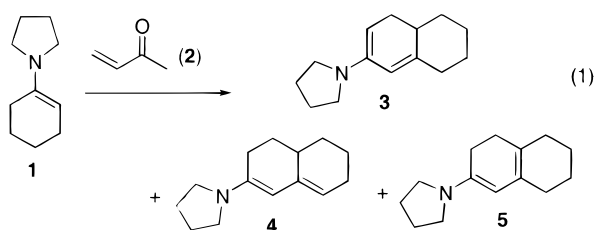
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ABSTRACT



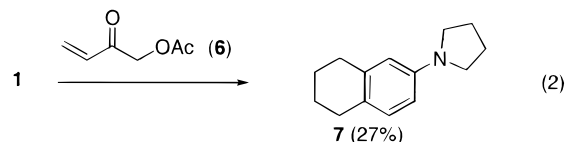
Condensation of pyrrolidine enamine of ketones with 1,4-diacetoxy-2-butanone provides a new, concise synthetic route to substituted benzenes, dihydroindenes, tetrahydronaphthalenes, and di- and octahydrophenanthrenes. The reaction produced modest yields with regiocontrol of the secondary amine substituent.

Condensation of enamines with α,β -unsaturated carbonyl compounds provides a convenient, one-step method for constructing nonaromatic rings.¹ This procedure has been used extensively in the synthesis of alkaloids, steroids, and terpenes.² One example of this transformation is the reaction of 1-(1-pyrrolidino)cyclohexene (**1**) with methyl vinyl ketone (**2**) to give hexahydronaphthalenes **3–5** in a combined yield of 78% (eq 1).³



Recently, we found that the reaction of enamine **1** with 1-acetoxy-3-buten-2-one (**6**)⁴ gave a single product, 6-(1-pyrrolidino)-1,2,3,4-tetrahydronaphthalene (**7**), in 27% isolated yield (eq 2). The observed ¹H and ¹³C NMR chemical

shifts and the ¹H–¹H coupling constants for **7** documented the site of pyrrolidine substitution and that cyclization proceeded with aromatization. The finding that reaction of **1** with **6** yielded an aromatic product while the corresponding reaction with **2** did not indicated that the acetoxy moiety in **6** was necessary for the formation of the annulated benzene ring.



We attributed the modest yield of **7**, in part, to the lability of **6**. Compound **6** was observed to undergo polymerization during overnight storage at 0 °C.⁴ Accordingly, we determined whether 1,4-diacetoxy-2-butanone (**8**) could be employed in place of **6**. Reaction of **1** with **8** in benzene at

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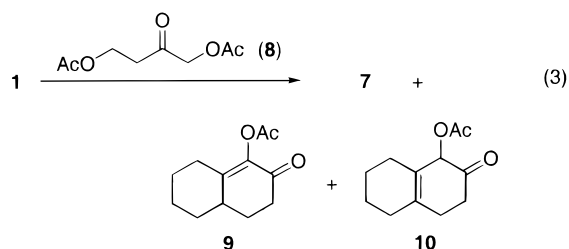
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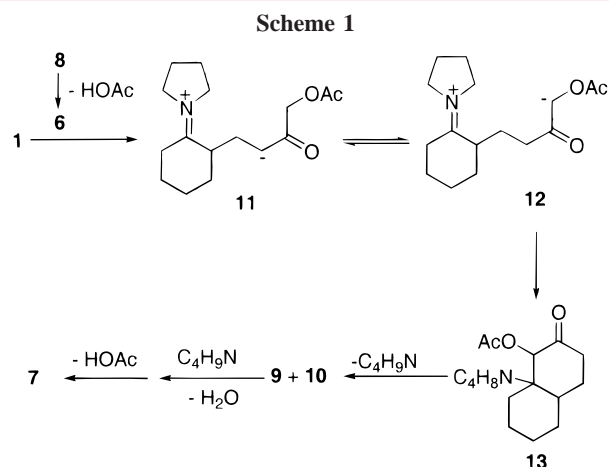
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room temperature afforded **7** (47% yield) along with a binary mixture (~7%) (eq 3). Spectroscopic analysis suggested that the binary mixture consisted of 1-acetoxy-4,4a,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (**9**) and 1-acetoxy-1,4,5,6,7,8-hexahydro-2(3*H*)-naphthalenone (**10**) in an approximately 2:1 ratio, respectively. Key to our assignments were the observation of two downfield ¹³C NMR signals, at 191.4 and 206.4 ppm, which we have attributed to the carbonyl carbons in **9** and **10**, respectively. Reducing the reaction time from 18 to 4 h decreased the yield of **7** to 3% and increased the combined yield of **9** and **10** to approximately 41%.



These initial findings suggested a pathway for the formation of **7** from **1** and **8** (Scheme 1). Michael addition of



enamine **1** to the in situ generated **6** gives zwitterion **11**. This species is in equilibrium with **12**, which cyclizes to **13**. Loss of pyrrolidine from **13** generates **9** or **10**. Condensation of pyrrolidine with the newly formed ketone **9** or **10** and loss of H₂O and HOAc provides the aromatic derivative **7**. This pathway is an extension of an earlier route proposed for the formation of compounds **3–5**.³

Attempts to further improve the yield of **7** were unsuccessful. Higher temperatures (60 °C) and longer reaction times (24 h) did not improve the yield, and inclusion of pyrrolidine (3 equiv) led to only trace amounts of **7**.⁵

The generality of this one-step, aromatic annulation procedure was investigated (Table 1). Ketones, varying in

(5) Compound **8** is unstable in the presence of amines (i.e., pyrrolidine, triethylamine, DBU). 1,7-Diacetoxy-3-methylene-2,6-heptanedione was obtained in 50% yield when a benzene solution of **8** and triethylamine (1 equiv) was stirred at room temperature (1 h).

Table 1. Products from Pyrrolidine Enamines of Ketones and **8**

entry	starting ketone	enamine(s)	product (yield %) ^a
1	14	15	16 (34)
2	17	18	19 (28)
3	20	21	22 (60)
4	23	24a , 24b	25 (47)
5	26	27	28 (42)
6	29	30	31 (41)
7	32	33	34 (65)
8	35	36a , 36b	37 (35)

^a Isolated yields based on starting ketones.

structure, were used to generate the corresponding aromatic derivatives. For ketones in entries 1–6, the corresponding enamine was prepared by refluxing (3 h) an anhydrous benzene solution of the ketone (1–2 mmol), pyrrolidine (2 equiv), and catalytic amounts of *p*-toluenesulfonic acid (PTSA) with a modified Dean–Stark apparatus.⁶ For ketones in entries 7 and 8, enamine formation required a longer reaction time (30 h) and a larger excess of pyrrolidine (10 equiv).⁷ The enamines obtained were concentrated in vacuo, and the crude enamines were directly added to an anhydrous benzene solution containing **8** (1.5 equiv). The reaction proceeded at room temperature (18 h), and the products were isolated by preparative TLC.

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We observed that acyclic (entry 1), carbocyclic (entries 2–4, 7, and 8), and heterocyclic (entries 5 and 6) ketones underwent aromatization upon treatment with **8**. The isolated yields are based on the starting ketones and were from 28 to 65%. Interestingly, we observed only a single product for ketones **23** (entry 4)⁸ and **35** (entry 8) even though the ¹H and ¹³C NMR spectra for the corresponding enamines **24** and **36**, respectively, showed the presence of two isomers. Products **25** and **37**, obtained in these reactions, were derived from the major enamine isomers **24a** and **36a**, respectively. Attempts to condense the pyrrolidine enamine from *N*-methyl-4-piperidinone with **8** failed to give a cycloadduct.

In conclusion, we have found a concise enamine-induced benzoannulation method that affords substituted benzene,

dihydroindene, tetrahydronaphthalene, and di- and octahydro-phenanthrene compounds. The reaction produced modest yields with regiocontrol of the secondary amine substituent.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **7**, **9**, **10**, **16**, **19**, **22**, **25**, **28**, **31**, **34**, and **37**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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